

**Appl. No.** : 10/035,977  
**Filed** : December 26, 2001

### **DELETION OF INVENTORS**

Please correct the inventorship under 37 CFR §1.48(b) by removing the following inventors from the present application:

Luc Desnoyers, Dan L. Eaton, Timothy L. Stewart and Zemin Zhang.

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### REMARKS

Upon entry of the foregoing amendments to the specification, the title has been amended. Also, the specification has been amended as shown above to remove URLs from the specification. No new matter has been added by the amendments to the title or the specification.

Claims 22-30, 32-35 and 38-41 are pending. Claims 31 and 36-37 have been cancelled. Claims 22-30, 32-33 and 35 have been amended to remove reference to the Figures. Claims 22-27, 30 and 35 have been further amended to specify the particular amino acid sequence of the "extracellular domain." Support for this amendment is found, for example, in Figure 26. Also, Claims 22-26 and 35 have been amended to add the limitation that the claimed nucleic acids encode polypeptides that have the ability to induce mesangial cell proliferation. Support for this amendment is found in Example 41 on page 168, describing a mesangial cell proliferation assay (Assay #92). Also, Claim 35 has been amended to recite the specific stringent hybridization conditions. The amendment to Claim 35 is supported by the specification at page 80, lines 10-14. Thus, no new matter is added by the amendments and the claims are fully supported by the specification as originally filed.

Applicants respond below to the specific rejections raised by the PTO in the Office Action mailed March 10, 2005. For the reasons set forth below, Applicants respectfully traverse.

#### **Correction of Inventorship under 37 CFR §1.48(b)**

Applicants request that several inventors be deleted, as these inventors' inventions are no longer being claimed in the present application as a result of prosecution. The fee as set forth in § 1.17(i) is submitted herewith.

#### **Information Disclosure Statement**

The Examiner states that the previously-filed information disclosure statements have been considered, but do not give sufficient identifying information to determine if the sequences constitute prior art.

Applicants submit herewith an Information Disclosure Statement that includes more detailed information regarding the BLAST results, including the publication date of the relevant sequences.

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### **Specification**

The Examiner states that a new title is required that is more clearly indicative of the invention to which the claims are directed. The title has been amended to recite "NUCLEIC ACIDS ENCODING POLYPEPTIDES THAT INDUCE CELL PROLIFERATION."

Also, the Examiner states that the specification should be reviewed for the recitation of improper hyperlinks, and that all such recitations should be deleted or amended. Applicants have amended the specification to address the Examiner's concern. In particular, Applicants have replaced the hyperlinks with text that describes the location of the websites. The amended text no longer constitutes browser executable code.

### **Rejection under 35 U.S.C. §101 - Utility**

The Examiner rejects Claims 22-41 under 35 U.S.C. §101 as lacking utility because allegedly the claims are not supported by a specific and substantial asserted utility, or a well established utility. The Examiner argues that the claimed invention is incomplete. The Examiner argues the claimed nucleic acids, and their encoded polypeptides, lack utility. The Examiner indicates that the specification asserts two specific utilities for the polypeptides encoded by the claimed nucleic acids based upon positive results in two assays. However, the Examiner argues that neither utility is substantial.

### **Utility – Legal Standard**

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." (1) A utility is "specific" when it is particular to the subject matter claimed. (2) With regard to substantial utility, "[a]ny reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility." (M.P.E.P. 2107.01). (3) "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record ... that is probative of the Applicant's assertions." (M.P.E.P. 2107 II(B)(1)(ii)). Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed,

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or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true.** The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Here, the claimed nucleic acids encode polypeptides that have at least one asserted utility that is specific, substantial, and credible. For example, the encoded polypeptides have utility based upon Example 41 on page 168, which describes a mesangial cell proliferation assay. Example 41 shows that certain polypeptides act to induce proliferation of mesangial cells, and therefore, are useful for the treatment of various kidney disorders, for example, those associated with decreased mesangial cell functions, such as, Berger disease or other nephropathies associated with Schönlein-Henoch purpura, celiac disease, dermatitis herpetiformis or Crohn disease. As mentioned in Example 41, PRO4380 is one of polypeptides that tested positive in the assay.

The ability to induce mesangial cell proliferation is specific or particular to the PRO4380 polypeptides, and is not an ability common to all peptides generally. Also, the utility is

substantial as treatment of the above-mentioned disorders provides a public benefit. Finally, one of ordinary skill in the art would recognize that the scientific assay results of Example 41 support the credibility of the utility assertion. Thus, the PRO4380 polypeptides and the nucleic acids that encode them are useful.

Nevertheless, the Examiner argues that Example 41 (Assay #92; page 168) fails to provide a substantial utility for the encoded polypeptides. In support, the Examiner relies upon an article by Rovin et al. (*Kidney Int'l*, 61:1293-1302, 2002). The Examiner reasons that Rovin et al. performed an assay that is similar to the assay of Example 41, and that according to Rovin et al., a 21% increase in proliferation above control is not statistically significant. Based upon that, the Examiner argues that a 15% increase in proliferation, as shown in Applicants' Example 41, must not be statistically significant. Therefore, the Examiner concludes that "Rovin et al. indicates that PRO4380 is not useful in the proliferation of kidney mesangial cells."

Respectfully, the article by Rovin et al. has been misunderstood or misinterpreted by the Examiner, and does not rebut the utility of the claims based upon Example 41. The passage from Rovin et al. does not indicate that 21% greater proliferation is not scientifically useful, important or significant, but instead indicates that that particular data point (21%) is statistically unreliable due to statistical errors.

The passage from Rovin et al. relied upon by the Examiner states:

There was a small increase in proliferation index (21%) in response to 5  $\mu\text{mol/L}$  ciglitazone, but this *did not reach significance*. (emphasis added).

This passage does not indicate that proliferation of 21% is not significant in terms of utility or scientific significance. Rather, the passage refers to whether the particular data point is statistically reliable or significant in terms of statistical error. In other words, "significance" as used in the cited passage refers to whether there is an overlap or non-overlap of standard deviations or errors in the data set. If there is an overlap between the control data point and the 5  $\mu\text{mol/L}$  data point, then it is possible that there is no difference in proliferation between the control and the compound at 5  $\mu\text{mol/L}$ , thus, that data point cannot be said to be reliable or significant. In the case of the data set showing a 21% increase, those data in fact are not statistically significant because the statistical error in their measurement overlaps with the statistical error of the control set. This is supported by reference to Figure 2A. As seen in Figure 2A, the error bars of the data point at 5  $\mu\text{mol/L}$  overlap with the error bar range of the adjacent

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data point. Therefore, the 5  $\mu\text{mol/L}$  data point was not statistically reliable or significant because of the amount of statistical error associated with the data point. This does not mean that an increase of proliferation of 21% is not scientifically useful, important or significant, but means that Rovin's particular measurement of 21% may be incorrect or erroneous due to the amount of error for that data point. The fact that a single data point reported by Rovin et al. had excessive statistical error such that it "did not reach significance," does not mean that any other data point, including Applicants' data, are statistically insignificant, much less lacking in scientific utility.

Interestingly, the two sentences immediately following the passage relied upon by Examiner do not support the Examiner's reasoning:

Similar results were found when troglitazone was used (Fig. 2B). Cell death occurred at concentrations greater than 15  $\mu\text{mol/L}$ , and there was as small, but *significant* increase in proliferation index (18%) using 10  $\mu\text{mol/L}$  troglitazone. (emphasis added).

Applicants assert that the term "significant" as used in Rovin et al. refers to whether the data are statistically reliable in terms of standard deviations or errors associated with the data point. This is demonstrated by Figure 2B which shows that at 10  $\mu\text{mol/L}$  there was no error bar overlap with the control data point. Thus, that particular  $\mu\text{mol/L}$  data point was statistic reliable or "significant."

Therefore, Rovin et al. does not contradict the utility of the claims based upon Example 41. Further, Rovin et al. provides no reasons that would lead one skilled in the art to question the objective truth of the statement of utility or its scope. As demonstrated by Example 41, PRO4380 induced a significant increase in cell proliferation. Thus, Applicants assert that person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true based upon the results of Example 41. For the reasons discussed above, the claimed subject matter has a specific, substantial and credible utility.

Therefore, Applicants respectfully request reconsideration and withdrawal of the instant rejection under 35 U.S.C. § 101.

#### **Rejections under 35 U.S.C. §112, first paragraph – Enablement**

The Examiner rejected Claims 22-41 under 35 U.S.C. § 112, first paragraph. According to the Examiner, because the claimed invention is not supported by either a substantial asserted

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utility or a well established utility, one of skill in the art would not know how to use the invention.

Applicants submit that in the above discussion of the rejection under 35 U.S.C. § 101, Applicants have established a substantial, specific, and credible utility for the claimed nucleic acids. Specifically, the claimed nucleic acids encode polypeptides that have utility in inducing mesangial cell proliferation.

The Examiner further rejects the variant claims arguing that “[e]ven if PRO4380 had utility and were enabled, enablement would not be commensurate in scope with claims 22-27, 30-31, and 35-[41], because the specification does not reasonably provide enablement for nucleic acids 80, 85, 90, 95 or 99% identical to SEQ ID NO:56, nor which encode a protein 80, 85, 90, 95 or 99% identical to SEQ ID NO:57, nor nucleic acids which hybridize to any of the above.”

As set forth above, Claims 22-26 and 35 have been amended to recite the functional limitation “wherein said isolated nucleic acid encodes a polypeptide that has the ability to induce mesangial cell proliferation.” In view of this, the specification teaches how to make and use the claimed subject matter. Specifically, the specification at page 109, line 7 to page 111, line 16, describes how to make variant polypeptides and the nucleic acids encoding them. The specification at pages 113, line 21 teaches how to isolate the nucleic acids encoding the PRO polypeptides. Also, the specification at pages 114-126 and in the examples teaches various uses for the nucleic acids that encode the PRO molecules. Furthermore, one of skill in the art would know how to follow Example 41 to assay for the claimed function in the encoded polypeptides. Based upon that teaching and the above-established utility for the claimed subject matter, one skilled in the art would know how to make and use the full scope of the claimed subject matter.

Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection under 35 U.S.C. § 112, first paragraph.

**Rejections under 35 U.S.C. §112, first paragraph – Deposit Requirements**

Claims 22-41 are rejected as not complying with the enablement requirement, since the deposit requirements were not met. The Examiner requests a statement that “the deposit will be maintained for a term of at least 30 years and at least five (5) years after the most recent request for the furnishing of sample of the deposit was received by the depository.”

Respectfully, this requirement has already been met. As noted by the Examiner, the deposit was made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). However, the Examiner argues that this statement only provides partial compliance with the deposit requirement and requests the above statement. Applicants assert that they have fully complied with the requirement by stating that the deposit was made under the provisions of the Budapest Treaty because deposit under the Treaty universally requires that the depositor agree not to withdraw the deposited material for a period of five years after the most recent request for a sample, and in any case at least 30 years after deposit (per Rule 9.1).

Nonetheless, enclosed is a Declaration under 37 C.F.R. §1.808 that states that the deposit will be maintained for a term of at least 30 years and at least five (5) years after the most recent request for the furnishing of sample of the deposit was received by the depository.

**Rejections under 35 U.S.C. §112, first paragraph – Written Description**

The Examiner asserts that Claims 22-27, 30-31 and 35-41 contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. In particular, the Examiner argues that “[t]he claims do not require that the claimed polynucleotide encode a particular protein, nor that any protein encoded thereby possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature.”

**The Legal Standard for Written Description**

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure “reasonably conveys to artisan that the inventor had possession at that time of the later claimed subject matter.” *In re Kaslow*, 707 F.2d 1366, 1375, 2121 USPQ 1089, 1096 (Fed. Cir. 1983); *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis. *See e.g., Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991). The factual determination in a written description analysis depends on the nature of the invention and the



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amount of knowledge imparted to those skilled in the art by the disclosure. *Union Oil v. Atlantic Richfield Co.*, 208 F.3d 989, 996 (Fed. Cir. 2000).

Applicants have amended Claims 22-26 and 35 to recite that the claimed variant nucleic acids “encode a polypeptide that has the ability to induce mesangial cell proliferation.” Accordingly, Applicants maintain that the claims recite sufficient distinguishing characteristics for the claimed genus of nucleic acids. Based upon the detailed description of the cloning and expression of variant nucleic acids encoding PRO4380 polypeptides, the description of the assay in Example 41, the actual reduction to practice of sequences SEQ ID NOs: 56 and 57, and the functional recitation in the instant claims, Applicants submit that one of skill in the art would recognize that Applicants possessed the claimed nucleic acids. Hence, Applicants respectfully request that the PTO reconsider and withdraw the written description rejection under 35 U.S.C. §112.

**Rejections under 35 U.S.C. §112, second paragraph**

The Examiner has rejected Claims 22-41 under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that “[c]laims that recite ‘extracellular domain’ of the protein are indefinite as no extracellular domain has been described.” Further according to the Examiner, if the polypeptide possesses an extracellular domain, the recitation of “the extracellular domain ... lacking its associated signal sequence” is indefinite because a signal sequence is general not considered to be part of an extracellular domain. Finally, the Examiner argues that the claims reciting that the claimed nucleic acid “hybridizes to” another sequence, such as Claim 35, are indefinite as there is no limiting definition of such in the specification.

Figure 26 discloses that the protein includes transmembrane domains at amino acids 273-292. The claims have therefore been amended to recite the specific region comprising the extracellular domain, namely, amino acids 293-507. Furthermore, Claims 22-27 have been amended and Claim 31 cancelled in order to delete reference to the “signal peptide” in connection with the “extracellular domain.”

With regard to hybridization, Claim 35 has been amended to recite the particular stringent conditions and to include a functional limitation.

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Applicants therefore request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

**Rejection under 35 U.S.C. §102 – Anticipation**

***Discussion of Ruben et al.:***

The Examiner rejects Claims 22-27, 29, 31 and 35-41 as anticipated under 35 U.S.C. § 102(a) by Ruben et al. (WO 99/58660) (hereinafter Ruben), which was published on November 18, 1999. The Examiner states that Ruben teaches a nucleic acid sequence (SEQ ID NO: 31) that is 95.3% identical to SEQ ID NO: 56 of the instant application, and therefore anticipates the claims. Applicants respectfully traverse.

As an initial matter, Applicants point out that Claims 36 and 37 have been cancelled. Therefore, the rejection of those claims will not be discussed further in connection with the rejections under § 102.

Attached herewith is the Declaration of Audrey Goddard, Paul J. Godowski, Austin L. Gurney, James Pan, Colin K. Watanabe and William I. Wood under 37 C.F.R. §1.131 (referred to hereafter as “the Declaration of Goddard et al.”), which establishes that the presently claimed invention antedates the publication date of Ruben. The Declaration of Goddard et al. establishes that the presently claimed subject matter was conceived of and reduced to practice prior to the publication date of Ruben, November 18, 1999. Thus, Applicants respectfully submit that the cited reference is not available as prior art, and request that the rejections under 35 USC §102(a) be withdrawn.

As set forth in 37 C.F.R. § 1.131, a patent applicant “may submit an appropriate oath or declaration to establish invention of the subject matter of the rejected claim prior to the effective date of the reference or activity on which the rejection is based.” *See also*, M.P.E.P. § 715. “The affidavit or declaration must state FACTS and produce such documentary evidence and exhibits in support thereof as are available to show conception and completion of the invention in this country ... at least conception being at a date prior to the effective date of the reference.” *See* M.P.E.P. § 715.07 (emphasis in original). The showing of facts must be sufficient to show “conception of the invention prior to the effective date of the reference coupled with due diligence from prior to the reference date to a subsequent (actual) reduction to practice.” *See id.*

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Ruben was published on November 18, 1999. Ruben is cited as a 102(a) reference because it allegedly discloses a nucleic acid sequence that is 95.3% identical to the sequence of SEQ ID NO: 56. However, as set forth below, Applicants were in possession of SEQ ID NO:56 prior to the publication date of Ruben.

The Declaration and attached Exhibit A demonstrate that the claimed subject matter, including a nucleic acid having the sequence of SEQ ID NO:56, was conceived by Applicants prior to November 18, 1999. Furthermore, as evidenced by the Declaration and Exhibit B, Applicants reduced the subject matter of the claims to practice from prior to the publication date of Ruben, by performing assays to confirm the function of the encoded polypeptide. Therefore, Applicants possessed as much of the claimed subject matter prior to the publication date of Ruben et al. Therefore, Ruben does not anticipate.

***Discussion of AI939620:***

The Examiner has rejected Claims 35-37 as anticipated under 35 U.S.C. § 102 by NCBI locus AI939620 (December 13, 1999). According to the Examiner, AI939620 discloses approximately 576 nucleotides that are complementary and will hybridize to a portion of SEQ ID NO:56. However, AI939620 was not publicly available until December 13, 1999. As discussed fully above, Applicants conceived of and reduced the claimed subject matter to practice prior to December 13, 1999. Therefore, AI939620 does not anticipate Claim 35.

***Discussion of: WO 98/20165, WO 98/50552, U.S. Pat. Nos. 6,783,961 & 6,084,088:***

The Examiner also has rejected Claims 35-37 as anticipated under 35 U.S.C. § 102 by each of WO 98/20165 (published May 14, 1998); WO 98/50552 (published November 12, 1998); U.S. Patent No. 6,783,961 (earliest possible priority to February 26, 1999); and U.S. Patent No. 6,084,088 (earliest possible priority to May 6, 1997). Applicants respectfully disagree.

As an initial matter, Applicants note that SEQ ID NO:56 has 2,242 total bases. The coding region extends from base 201 to base 1,721 for a total of 1,521 bases. The extracellular domain extends from base 1,077 to base 1,721. Respectfully, Claim 35 is not anticipated by any of the cited references because none disclose a nucleic acid sequence that meets all of the limitations of Claim 35.

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*WO 98/20165*

As set forth in the Office Action, WO 98/20165 discloses a sequence with 127 nucleotides, 126 of which are complementary to bases 2,017 - 2,143 of Applicants' SEQ ID NO:56. Thus, the cited sequence covers only about 5.6% of the total sequence of SEQ ID NO:56. Furthermore, the sequence does not cover any of the coding region of SEQ ID NO:56. As such, WO 98/20165 does not anticipate Claim 35 because it most likely will not hybridize to any of the claimed sequences under the specified hybridization conditions, and it does not encode a polypeptide that has the ability to induce mesangial cell proliferation.

*WO 98/50552*

Similarly, WO 98/50552 discloses a sequence with 64 nucleotides, 63 of which, according to the Examiner, are identical to bases 2,178 - 2,242 (3' terminus) of Applicants' SEQ ID NO:56. Thus, the cited sequence covers only about 2.8% of the total sequence of SEQ ID NO:56. Furthermore, the sequence does not cover any of the coding region of SEQ ID NO:56. As such, WO 98/50552 does not anticipate Claim 35 because it most likely will not hybridize to any of the claimed sequences under the specified hybridization conditions, and it does not encode a polypeptide that has the ability to induce mesangial cell proliferation.

*U.S. Patent No. 6,783,961*

U.S. Patent No. 6,783,961 discloses a sequence with 231 nucleotides, 230 of which, according to the Examiner, are identical to bases 66 - 296 of Applicants' SEQ ID NO:56. Thus, the cited sequence covers only about 10.3% of the total sequence of SEQ ID NO:56. However, the sequence of the '961 patent does not include any of the sequence that encodes the extracellular domain of SEQ ID NO:56. The cited sequence cover only 95 of the bases in the coding region including the signal peptide (approximately 6.2% of coding region including the signal peptide coding sequence) and only 16 bases of the coding region without the signal peptide (approximately 1.1%). As such, the '961 patent does not anticipate Claim 35 because it most likely will not hybridize to any of the claimed sequences under the specified hybridization conditions, and it does not encode a polypeptide that has the ability to induce mesangial cell proliferation.

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*U.S. Patent No. 6,084,088*

Finally, U.S. Patent No. 6,084,088 discloses a sequence with 61 nucleotides, which, according to the Examiner, are identical to bases 2182 - 2,242 (3' terminus) of Applicants' SEQ ID NO:56. Thus, the cited sequence covers only about 2.7% of the total sequence of SEQ ID NO:56. Furthermore, the sequence does not cover any of the coding region of SEQ ID NO:56. As such, the '088 patent does not anticipate Claim 35 because it most likely will not hybridize to any of the claimed sequences under the specified hybridization conditions, and it does not encode a polypeptide that has the ability to induce mesangial cell proliferation.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. §102.

### **Conclusion**

The present application is believed to be in condition for allowance, and an early action to that effect is respectfully solicited. Applicants invite the Examiner to call the undersigned if any issues may be resolved through a telephonic conversation.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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